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EXAMINER	
CHAKRABARTI, ARUN K	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

	Application No.	Applicant(s)
Office Action Summary	09/890,377	OLEK, ALEXANDER
	Examiner	Art Unit
	Janell Cleveland Taylor	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

DETAILED ACTION

Specification

1. Claims 1 and 19 have been amended.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-5, and 7-23 are rejected under 35 U.S.C. 103 (a) over Herman et al. (U.S. Patent 6,265,171 B1) (July 24, 2001) in view of Koster (U.S. Patent 5,605,798) (February 25, 1997).

Herman et al teach a method for the identification of cytosine methylation patterns in genomic DNA samples (Abstract) characterized in that:

a) a genomic DNA sample is treated chemically in such a way that cytosine and 5-methylcytosine react differently and a different base pairing behavior of the two products is obtained in the duplex (Examples 1- 2, and Column 23, line 66 to column 24, line 7 and column 5, line 33 to column 6, line 37 and Claim 1);

b) portions of the thus-treated DNA samples are enzymatically amplified (Example 2, Column 24, lines 4-27 and claim 1);

c) the amplified portions of the thus-treated DNA samples are bound to a surface (in this case polyacrylamide gels) (Figures 1 and 2 and Example 2);

d) a set of probes of different nucleobase sequences, each of which contains the dinucleotide sequence 5'-CpG-3' at least once, are hybridized to the immobilized DNA samples (Figure 1 and Example 2, Column 23, line 27 to column 24, line 3);

e) the non-hybridized probes are separated (inherently in this case by the Southern blot technique) (Example 2 and Figure 1);

Herman et al teach a method, further characterized in that the immobilized complementary oligonucleotide sequences contain modified bases, ribose or backbone units (Example 2, Figures 1 and 2).

Herman et al teach a method, further characterized in that the genomic DNA sample is propagated in b) in the form of several amplified fragments, so that at least 0.01 % of the total genome is amplified (Example 1).

Herman et al teach a method, further characterized in that the mixture of amplified DNA fragments is bound to a surface, on which a multiple number of different points is arranged, each of which can bind different portions of the amplified DNA sample (Figure 1).

Herman et al teach a method, further characterized in that a set of probes is used in d), which contains the dinucleotide sequence 5'-CpG-3' only once in each probe and the probes otherwise contain either no cytosine or no guanine bases (Column 18, SEQ ID No: 130).

Herman et al teach a method, further characterized in that a bisulfite solution is used together with other reagents for the specific or sufficiently selective conversion of cytosine to uracil (Column 6, lines 7-25 and Example 1, Column 22, lines 24-36).

Herman et al do not teach a method wherein the hybridized probes are analyzed in a mass spectrometer and the position of the probes on the sample holder permits a classification of the hybridizing DNA sample.

Koster teaches a method wherein the hybridized probes are analyzed in a mass spectrometer and the position of the probes on the sample holder permits a classification of the hybridizing DNA sample (Abstract, Examples 1-2, Figures 10-11, Column 4, lines 25-55, and claim 1).

Herman et al do not teach a method, further characterized in that one or more amplified genomic DNA fragments are immobilized in step c) by hybridization with complementary oligonucleotide sequences, which are covalently bound to the surface.

Koster teaches a method further characterized in that one or more amplified genomic DNA fragments are immobilized in step c) by hybridization with complementary oligonucleotide sequences, which are covalently bound to the surface (Figures 1 and 4 and Example 1 and Claim 4).

Herman et al do not teach a method, further characterized in that a covalent or electrostatic cross-linking of the genomic DNA fragments with the oligonucleotide bound to the surface results after hybridization.

Koster teaches a method, further characterized in that a covalent or electrostatic cross-linking of the genomic DNA fragments with the oligonucleotide bound to the surface results after hybridization (Figures 1-4 and Column 7, line 54 to column 8, line 60).

Herman et al do not teach a method, further characterized in that the hybridized probes are stripped from the immobilized amplified DNA samples before, after or by contact with a matrix.

Koster teaches a method, further characterized in that the hybridized probes are stripped from the immobilized amplified DNA samples before, after or by contact with a matrix (Column 10, line 65 to column 11, line 10).

Herman et al do not teach a method, further characterized in that the probes are nucleic acids, which bear one or more mass tags including charge tags.

Koster teaches a method, further characterized in that the probes are nucleic acids, which bear one or more mass tags including charge tags (Column 9, line 54 to Column 10, line 15 and Figure 6C).

Herman et al do not teach a method, further characterized in that the probes are modified nucleic acid molecules.

Koster teaches a method, further characterized in that the probes are modified nucleic acid molecules (Column 9, lines 54-67).

Herman et al do not teach a method, further characterized in that the modified nucleic acid molecules are PNAs, or alkylated phosphorothioate nucleic acids.

Koster teaches a method, further characterized in that the modified nucleic acid molecules are PNAs, or alkylated phosphorothioate nucleic acids (Column 9, lines 8-27).

.Herman et al do not teach a method, further characterized in that the probes are prepared by combinatory synthesis.

Koster teaches a method, further characterized in that the probes are prepared by combinatory synthesis (Column 9, lines 61-67).

Herman et al do not teach a method, further characterized in that different base structural units are labeled in such a way that the each of the probes synthesized from them can be distinguished from their mass in the mass spectrometer.

Koster teach a method, further characterized in that different base structural units are labeled in such a way that the each of the probes synthesized from them can be distinguished from their mass in the mass spectrometer (Figure 8).

Herman et al do not teach a method, further characterized in that the probes are prepared as sublibraries and these are provided with different mass and/or charge tags.

Koster teach a method, further characterized in that the probes are prepared as sublibraries and these are provided with different mass and/or charge tags (Column 10, lines 1-65).

Herman et al do not teach a method, further characterized in that matrix-assisted laser desorption/ionization mass spectrometry (MALDI) is conducted in f).

Koster teach a method, further characterized in that matrix-assisted laser desorption/ionization mass spectrometry (MALDI) is conducted (Column 10, line 66 to column 11, line 18 and Example 1 and Claims 11, 21, and 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the DNA diagnostic based on mass spectrometry of Koster in the method of detection of methylated nucleic acid using agents which modify unmethylated cytosine and distinguish modified methylated and unmethylated nucleic acids of Herman et al. since Koster states, "In addition, because the instant disclosed processes allow the nucleic acid fragments to be identified and detected at the same time by their specific molecular weights (an unambiguous physical standard), the disclosed processes are also much more accurate and reliable than currently available procedures (Column 4, lines 50-55)." An ordinary practitioner would have been motivated to combine and substitute the DNA diagnostic based on mass spectrometry of Koster in the method of detection of methylated nucleic acid using agents which modify unmethylated cytosine and distinguish modified methylated and unmethylated nucleic acids of Herman et al. in order to achieve the express advantages, as noted by Koster, of processes which allow the nucleic acid fragments to be identified and detected at the same time by their specific molecular weights (an unambiguous physical standard), and which are also much more accurate and reliable than currently available procedures.

4. Claim 6 is rejected under 35 U.S.C. 103 (a) over Herman et al. (U.S. Patent 6,265,171 B1) (July 24, 2001) in view of Koster (U.S. Patent 5,605,798) (February 25, 1997) further in view of Katouzian-Safadi et al. (Biochimie, (1994), Vol. 76, (2), pages 129-132).

Herman et al. in view of Koster teach the method of claims 1-5, and 7-23 as described above.

Herman et al. in view of Koster do not teach the method, further characterized in that the oligonucleotide bound to the surface contain 5-bromouracil structural units.

Katouzian-Safadi et al. teach the method, further characterized in that the oligonucleotide bound to the surface contain 5-bromouracil structural units (Summary and Results Section).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the oligonucleotide containing 5-bromouracil structural units of Katouzian-Safadi et al. in the mass spectrometric method of detection of methylated nucleic acid using agents which modify unmethylated cytosine and distinguish modified methylated and unmethylated nucleic acids of Herman et al in view of Koster since Katouzian-Safadi et al. state, "The substitution of thymine by 5-bromouracil in DNA increases the photocrosslinking yield, and reduces the direct damages to both DNA and protein (Summary, second sentence)." An ordinary practitioner would have been motivated to combine and substitute the oligonucleotide containing 5-bromouracil structural units of Katouzian-Safadi et al. in the mass spectrometric method of detection of methylated nucleic acid using agents which modify unmethylated cytosine and distinguish modified methylated and unmethylated nucleic

acids of Herman et al in view of Koster in order to achieve the express advantages, as noted by Katouzian-Safadi et al., of the substitution of thymine by 5-bromouracil in DNA , which increases the photocrosslinking yield, and reduces the direct damages to both DNA and protein.

5. Claim 24 is rejected under 35 U.S.C. 103 (a) over Herman et al. (U.S. Patent 6,265,171 B1) (July 24, 2001) in view of Koster (U.S. Patent 5,605,798) (February 25, 1997) further in view of Stratagene Catalog (1988, Page 39).

Herman et al. in view of Koster expressly teaches the claims 1-5, and 7-23 as described above in detail.

Herman et al. in view of Koster do not teach the motivation to combine all the reagents for identification of cytosine methylation patterns in a genomic DNA samples in the form of a kit.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine a suitable container, a sample holder for a mass spectrometer, all the reagents for identification of cytosine methylation patterns in a genomic DNA samples , as taught by Herman et al. in view of Koster into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram

amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control". (page 39, column 1).

Response to Amendment

6. In response to amendment, 112 (second paragraph) rejections are hereby withdrawn. However, 103 (a) rejections have been properly maintained.

Response to Arguments

7. Applicant's arguments filed on September 4, 2002 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant also argues that there is

no motivation to combine the references. This argument is not persuasive, especially in the presence of strong motivation provided by Koster since Koster states, "In addition, because the instant disclosed processes allow the nucleic acid fragments to be identified and detected at the same time by their specific molecular weights (an unambiguous physical standard), the disclosed processes are also much more accurate and reliable than currently available procedures (Column 4, lines 50-55)." This logic is applicable to all other 103 (a) rejections.

With regard to the lack of reasonable expectation of success regarding the combination of Herman and Koster reference and the use of agarose gel by Herman reference to detect a bound fragment of nucleic acid argument, The MPEP 2143.02 states

"Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. In re Rinehart , 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) (Claims directed to a method for the commercial scale production of polyesters in the presence of a solvent at superatmospheric pressure were rejected as obvious over a reference which taught the claimed method at atmospheric pressure in view of a reference which taught the claimed process except for the presence of a solvent. The court reversed, finding there was no reasonable expectation that a process combining the prior art steps could be successfully scaled up in view of unchallenged evidence showing that the prior art processes individually could not be commercially scaled up successfully.). See also Amgen, Inc. v. Chugai Pharmaceutical Co ., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir.), cert. denied , 502 U.S. 856 (1991) (In the context

of a biotechnology case, testimony supported the conclusion that the references did not show that there was a reasonable expectation of success. 18 USPQ2d at 1022, 1023.); In re O'Farrell , 853 F.2d 894, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.)."

There is no evidence of record submitted by applicant demonstrating the absence of a reasonable expectation of success. There is evidence in the Herman reference of the enabling methodology, the suggestion to modify the prior art, and evidence that a number of different and rapid identification of DNA methylation patterns in a CpG-containing nucleic acids were actually experimentally studied and found to be functional (Example 3). This evidence of functionality trumps the attorney arguments, which argues that Herman reference is an invitation to research, since Herman steps beyond research and shows the functional product.

Applicant argues that Herman reference does not teach the analysis of many methylation positions in parallel of the claimed invention. Applicant argues that the word "many" or "multiplexed" was not found in Herman reference and only the word "single" are found. Applicant argues that because Herman has a preferred embodiment of single primer sets, Herman is limited to the preferred embodiment. This argument is not persuasive. As MPEP 2123 states "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi,169 USPQ 423 (CCPA

1971)." MPEP 2123 also states " A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories , 10 USPQ2d 1843 (Fed. Cir. 1989)." It is clear that simply because Herman has a preferred embodiment, this embodiment does not prevent the reference from suggesting broader embodiments in the disclosure and that this does not constitute a teaching away. Although Herman reference uses single primer set to detect the methylated nucleic acids, the property of multiplexing is inherently present in this chemically and structurally identical molecule. For example, Herman teaches that rapid, fine mapping of methylation patterns throughout the CpG rich regions (Column 5, lines 20-22). Moreover, MPEP 2111 states, "Claims must be given their broadest reasonable interpretation. During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification". Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than it is justified. *In re Prater,* 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-51 (CCPA 1969)". In this case, fine mapping of methylation patterns throughout the CpG rich regions under any suitable conditions can be considered as the analysis of many methylation positions in parallel.

Similar logic is applicable to the applicant's argument that Herman does not teach amplification and Herman only teaches bisulfite sequencing of the individual fragments. Herman clearly teaches amplification (Example 1 and Column 6, lines 26 to Column 7, line 27). Similar

logic is applicable does not teach probes, it only teaches primers. It is obvious and well known in the art that a labeled primer can be used as a probe.

Similar logic is applicable to the applicant's argument that Koster does not teach charge tags and only teaches mass tags of the individual fragments. Koster inherently teaches systematic use of mass as well as charge tags as evident from the molecular ion peaks (Figures 1-11).

In view of the response to arguments, all previous 103(a) rejections are hereby properly maintained.

Conclusion

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D., whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237.

Arun Chakrabarti,

Patent Examiner,

September 17, 2002

W. Gary Jones
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